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Brief Communications

Serious Cutaneous Toxicities with Immune Checkpoint Inhibitors in the U.S. Food and Drug Administration Adverse Event Reporting System

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Abstract

Cutaneous toxicities frequently occurred with immune checkpoint inhibitors (ICIs), although clinical and pharmacological features are incompletely characterized. The U.S. Food and Drug Administration Adverse Event Reporting System was queried to describe ICI-related cutaneous toxicities, focusing on severe cutaneous adverse reactions (SCARs): Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. As compared with other anticancer drugs, a higher proportion of death (11.3% vs. 8.7%) and serious reports (42.7% vs. 34.6%) emerged for ICIs ($p < .05$). A higher frequency of coreported allopurinol and antiepileptics was recorded among 2,525 total SCARs (17% vs. 10%, ICIs and anticancer agents, respectively; $p < .05$). Mean times to onset were 47, 48, and 40 days (SJS, TEN, and DRESS, respectively), with comparable mean latency between monotherapy and combination regimens (41 days). This immune-related pattern advocates for long-lasting monitoring by oncologists and dermatologists. ***The Oncologist*** 2019;24:e1228–e1231

Introduction

Immune checkpoint inhibitors (ICIs), by blocking cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1) or its ligand (PDL1), can cause a unique set of immune-related adverse events (irAEs) [1]. Although these toxicities are usually manageable, fulminant and fatal events do occur [2], and this calls for closer collaboration among oncologists and other specialties to ensure personalized management [3].

Among the variegate irAEs derived from clinical trials, cutaneous toxicity is one of the most frequently observed, especially skin rash, pruritus, and vitiligo, which was also suggested to be a toxic effect associated with patient survival [4]. Sporadic case series have also described cutaneous eruptions, including bullous pemphigoid and severe cutaneous adverse reactions (SCARs), comprising Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [5].

Therefore, we characterized spectrum, timing, and other clinical features of cutaneous irAEs submitted to the largest publicly available repository of unsolicited reports, namely the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), focusing on SCARs.

Materials and Methods

Among more than 16 million FAERS reports as of June 2018, we examined cutaneous events in which at least one ICI (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab) was recorded as suspect.

Skin disorders were first described in terms of patient demographics (sex, age, country, outcome, type of reporter). A serious irAE was defined as causing death, being life-threatening, requiring hospitalization (initial or prolonged), or leading to disability or congenital anomaly.

FAERS also allows to perform disproportionality analysis, a validated concept in pharmacovigilance, to assess whether suspected drug-induced events are differentially reported with ICIs [6]. In this study, we carried out the so-called disproportionality analysis by therapeutic area, (i.e., we selected reports where at least one anticancer agent was recorded, as a proxy of neoplasia). This consolidated approach allows selection of a real-world oncological population with at least partially comparable risk factors (this mitigates confounding by indication) and provides a clinical perspective by comparing ICIs with other anticancer drugs. If an imbalance exists in the proportion of cutaneous events in subjects exposed to anti-PD1/PDL1 or anti-CTLA4 agents (cases) as compared with individuals receiving

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Table 1. Most frequent skin toxicities with immune checkpoint inhibitors

Signs and symptoms	Number of cases (ICIs/anti-PD1 and PDL1/anti-CTLA4)[a]	Percentage of serious cases (ICIs/anti-PD1 and PDL1/anti-CTLA4)	Anti-PD1 and PDL1 vs. other anticancer drugs (including anti-CTLA4), ROR (95% CI)	Anti-CTLA4 vs. other anticancer drugs (including anti-PD1 and PDL1), ROR (95% CI)
Skin rash or inflammatory dermatoses				
Acute febrile neutrophilic dermatosis	11/1/10	45/0/50	NA	**2.54 (1.35–4.70)**
Alopecia areata	5/5/0	38/36/47	4.77 (1.81–12.59)	NA
Autoimmune dermatitis	12/4/10	50/100/40	7.92 (2.44–25.73)	**54.42 (14.98–197.77)**
Cutaneous sarcoidosis	11/11/3	36/36/67	**9.77 (4.61–20.68)**	NA
Dermatitis	124/73/72	44/53/39	1.20 (0.95–1.52)	**3.26 (2.57–4.13)**
Dermatitis psoriasiform	28/27/1	61/63/0	**6.38 (4.13–9.86)**	NA
Dermatomyositis	32/24/10	56/67/40	2.86 (1.87–4.37)	3.27 (1.74–6.18)
Erythema multiforme	79/75/12	76/76/83	**2.34 (1.85–2.97)**	1.03 (0.58–1.82)
Erythema nodosum	12/4/9	50/50/56	0.44 (0.16–1.18)	**2.72 (1.40–5.30)**
Pruritus	824/576/322	34/37/34	1.11 (1.02–1.21)	1.72 (1.54–1.93)
Rash maculopapular	201/150/93	62/59/75	2.21 (1.87–2.61)	3.77 (3.06–4.65)
Rash pruritic	160/99/73	33/39/29	1.01 (0.83–1.24)	**2.06 (1.63–2.60)**
Perivascular dermatitis	5/4/1	20/25/0	NA	NA
Skin rash and inflammatory dermatoses				
Leukoderma	46/46/8	57/57/75	**23.25 (9.24–58.51)**	11.10 (5.22–23.60)
Lichen planus	32/31/2	31/32/50	**5.79 (3.88–8.63)**	NA
Lichenoid keratosis	59/55/10	31/29/60	**8.15 (5.92–11.22)**	4.07 (2.15–7.70)
Psoriasis	131/125/10	37/38/20	**2.12 (1.77–2.55)**	0.46 (0.25–0.87)
Skin depigmentation	12/12/3	33/33/33	**2.22 (1.23–4.02)**	NA
Skin hypopigmentation	12/11/5	42/45/80	2.36 (1.27–4.39)	2.95 (1.20–7.22)
Vitiligo	101/80/43	25/20/33	12.07 (8.93–16.30)	17.83 (12.62–25.20)
Bullous dermatoses				
Drug eruption	86/81/21	65/64/6	1.79 (1.42–2.24)	1.27 (0.82–1.96)
Pemphigoid[b]	123/115/19	46/46/53	**12.47 (9.67–16.09)**	5.65 (3.53–9.03)
SCARs[c]				
Drug reaction with eosinophilia and systemic symptoms	39/35/8	44/43/50	1.69 (1.20–2.38)	1.06 (0.53–2.13)
Stevens-Johnson Syndrome	96/87/20	76/77/65	1.68 (1.35–2.08)	1.06 (0.68–1.64)
Toxic epidermal necrolysis	66/57/13	91/91/92	1.84 (1.41–2.41)	1.15 (0.67–1.99)

Only adverse events with statistically significant ROR in at least one analysis, and at least five cases are shown. Largest differences in terms of ROR values (at least 2-fold) between anti-CTLA4 and anti-PD1 and PDL1 drugs are shown in bold.

[a]The sum of the number of cases for the different ICI regimens may be higher than the total number of cases for the drug class because a patient may have received more than one ICI (combination regimen).

[b]Five cases of pemphigus were also reported without reaching statistical significance (anti-PD1 and PDL1 were recorded in all cases, whereas anti-CTLA4 agents were recorded in two cases).

[c]Only one case of acute generalized exanthematous pustulosis was reported with anti-PD1 and PDL1 drugs. A total number of 191 SCARs were initially retrieved and used in the disproportionality analysis; 190 cases were finally retained after the exclusion of one case of SJS because of biological implausible onset (see text for details).

Abbreviations: CTLA4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; NA, not applicable (because of low number of cases, less than 5); PD1, programmed cell death 1; PDL1, programmed cell death ligand 1; ROR, reporting odds ratio; SCAR, severe cutaneous adverse reaction.

other oncological drugs (non-cases), an association can be hypothesized. Through this so-called case/non-case approach, the reporting odds ratio (ROR) with relevant 95% confidence interval (CI) was calculated and deemed significant when the lower limit of the 95% CI of the ROR >1, with at least five cases reported, to reduce the likelihood of false positives [6].

Finally, SCARs were characterized in terms of mortality (i.e., death as reported outcome) onset (in relation to therapeutic regimen, i.e., monotherapy anti-CTLA4 or anti-PD1/PDL1 drugs vs. combined ICIs), known culprit agents among concomitant drugs (allopurinol and antiepileptics), and co-reported hepatobiliary disorders (known to often occur with

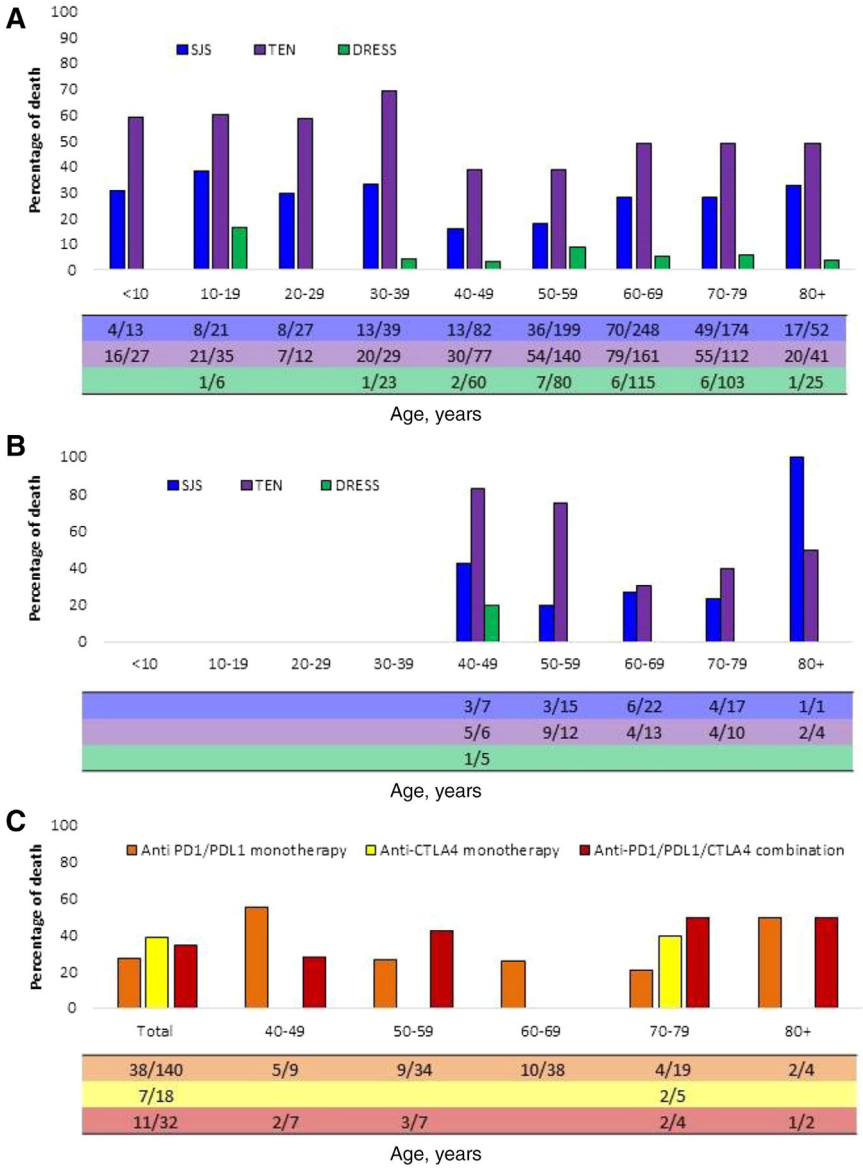

Figure 1. Relationship between age and reporting of death on Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) with other anticancer drugs **(A)** and immune checkpoint inhibitors (ICIs) **(B)**, also depending on the ICI therapeutic regimen **(C)**. Bars are presented as percentages; crude numbers provided below each age group provided the ratio between fatal and nonfatal cases (i.e., cases where death was recorded as outcome). Abbreviations: CTLA4, cytotoxic T-lymphocyte antigen 4; PD1, programmed cell death 1; PDL1, programmed cell death ligand 1.

DRESS). Categorical variables were compared between ICIs and anticancer drugs using chi-square testing.

Results and Discussion

We collected 4,618 cutaneous events with ICIs (9.8% of total ICI reports; 58% from U.S.; 38% submitted by consumers; 55% in males), as compared with 134,488 skin reports for other anticancer drugs (34% in males). Adults aged 50–79 were the most commonly represented (51.7% vs. 48.2%, ICIs and other anticancer agents, respectively), with a higher proportion of reported death (11.3% vs. 8.7%, $p < .05$) and serious events (42.7% vs. 34.6%, $p < .05$).

Rash was the most frequently reported sign ($n = 1,489$), without meeting criteria for possible association (ROR, 0.91; 95% CI, 0.87–0.96), followed by pruritus ($n = 824$) with significant ROR (1.30; 1.21–1.39). A synopsis of disproportionality analysis is provided in Table 1. Alterations of skin surface and color (especially leukoderma, lichen planus, lichenoid keratosis, psoriasis) were more frequently reported with anti-PD1/PDL1 agents (except for vitiligo, also recorded for anti-CTLA4 drugs), whereas rash and inflammatory dermatoses showed a mixed pattern of reporting: cutaneous sarcoidosis, erythema multiforme, and dermatitis psoriasiform were largely reported with anti-PD1/PDL1 agents; acute febrile neutrophilic dermatosis and erythema nodosum were almost exclusively documented for anti-CTLA4 medications. Bullous dermatoses, especially pemphigoid, were mainly reported with anti-PD1/PDL1 agents.

Overall, 2,525 SCARs were retrieved: 191 recording ICIs and 2,334 with other anticancer drugs. Allopurinol and antiepileptics were recorded in 17% versus 10% (ICIs and anticancer agents, respectively, $p < 0.05$). Specifically, for ICIs,

allopurinol was coreported in 3.1% (n = 3), 15.2% (n = 10), and 5.1% (n = 2) of SCARs; antiepileptics in 10.4% (n = 10), 9.1% (n = 6), and 7.7% (n = 3) of cases (SJS, TEN, and DRESS, respectively). For anticancer drugs, corresponding proportions were 5.0% (n = 62), 5.5% (n = 40), and 10.9% (n = 54) for allopurinol; 2.7% (n = 34), 5.1% (n = 37), and 6.3% (n = 31) for antiepileptics.

After excluding a single case of SJS because of biological implausible onset time (844 days), 190 SCARs with ICIs were finally retained: DRESS (n = 39) was mostly prevalent in men (72%) aged 50–59 years (41%), whereas SJS (n = 95) and TEN (n = 66) were prevalent in patients 60–69 years of age (23.2% and 19.7%, respectively), with an overall mortality proportion of 2.6% (1 case), 18%, and 36% (DRESS, SJS and TEN, respectively). Although no statistically significant difference emerged (p = .417), a higher fraction of death emerged for TEN in individuals aged 40–59, as compared with other anticancer drugs (>70% vs. <40%; Fig. 1A, B).

Mean time to onset was 47 days for SJS, 48 days for TEN, and 40 days for DRESS (calculated for 51, 28, and 28 cases with available and valid information, respectively), with 251, 197, and 164 days as longest recorded latencies (SJS, TEN, and DRESS, respectively). Stratification according to ICI regimens (calculated for 104 cases) found a comparable mean onset between therapeutic combination (41 days) and monotherapies (45 and 65 days for anti-PD1/PDL1 agents and anti-CTLA4 drugs, respectively) and a similar proportion of mortality (Fig. 1C). Hepatobiliary disorders were concomitantly identified in 11 (11.6%), 5 (7.6%), and 5 cases (12.8%) for SJS, TEN, and DRESS, respectively.

Overall, our data (a) confirmed the variegate pattern of cutaneous toxicity [6], including nonspecific manifestations such as rash maculopapular and pruritus, as well as serious irAEs and SCARs, thus making a timely consultation with dermatologist pivotal to minimize unnecessary drug interruption [3]; (b) found a differential reporting between anti-PD1/PDL1 drugs (psoriasis, dermatitis psoriasiform, pemphigoid, and cutaneous sarcoidosis) and anti-CTLA4 medications (acute febrile neutrophilic dermatosis and erythema nodosum) [5, 7]; and (c) recorded a high proportion of death in young adults with SCARs, especially TEN (83% in adults aged 40–49), with a delayed latency as compared with recently published data on anticancer drugs (mean 46 vs. 18 days [8]), in keeping with immune-related basis. This conflicts with the algorithm of drug causality for epidermal necrolysis (ALDEN), which was validated on heterogeneous drugs and suggested that late events are unlikely to be drug related [9]): we invite clinicians to submit complete high-quality reports, as recommended by the Side Effect Reporting in Immuno-Oncology (SERIO) working group [10]. Intriguingly, ICI combination was not characterized by higher fatality or shorter latency in comparison with monotherapy regimens.

Conclusion

Notwithstanding limitations (including inability to firmly infer causality, risk ranking, existence of missing data, lack of exposure data and clinical elements such as biopsy, residual confounders such as channeling bias), this study characterized worldwide cutaneous irAEs with ICIs in FAERS and found a large proportion of serious irAEs. As compared with other anticancer drugs, we found a higher proportion of fatal SCARs, a higher frequency of coreported allopurinol and antiepileptics, and an unexpectedly delayed onset, which advocates for long-lasting monitoring by oncologists and dermatologists. Further research is needed to define patient- and drug-related specific risk factors and optimal management strategies.

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